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SCIENTIFIC DATA REVIEWS
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDE AND TOXIC SUBSTANCES

MEMORANDUM

Date: April 8, 2008

SUBJECT: **Ingredient:** Glufosinate Ammonium **Title:** Request to Waive Requirement for Glutamine Synthetase Measurements and Other Data Requirements

PC Code: 128850
MRID No.: See Table
Petition No.: None
Assessment Type: None
TXR No.: 0054838

DP Barcode: 328229
Registration No.: None
Regulatory Action: None
Reregistration Case No.: None
CAS No.: None

FROM: Lisa Austin, Ph.D., Toxicologist
Registration Action Branch (RAB) 1
Health Effects Division 7509P

THROUGH: P.V. Shah, Ph.D., Acting Branch Chief
Inerts
Registration Division 7505P

Jess Rowland, Branch Chief
SIMB
Health Effects Division 7509P

Vicki Dellarco, Ph.D., Sr. Science Advisor
Immediate Office
Health Effects Division 7509P

Ray Kent, Branch Chief
Reregistration Branch 4
Health Effects Division 7509P

TO: William Donavan, Ph.D., Chemist
Reregistration Branch 3
Health Effects Division 7509P

I. CONCLUSIONS

The Health Effects Division's (HED) Hazard Identification Assessment Committee (HIARC) recommended conducting a number of toxicity studies (mentioned below) with Glufosinate Ammonium. In response to this request, Bayer Crop Science submitted additional data and rationale to support data waivers for these studies. Following the evaluation of the submitted data HED has concluded that it is appropriate to grant waivers of these studies. Consequently, no additional toxicity studies are required at this time.

II. ACTION REQUESTED

HED was asked to evaluate additional data and rationale submitted by the Registrant to support data waivers for the studies, stated below, that were previously recommended by HIARC.

III. BACKGROUND

The Health Effects Division's Hazard Identification Assessment Committee (HIARC) identified the following studies as data gaps: 1) a comparative measurements of glutamine synthetase (GS) activity in the brain, kidney and liver in young and adult animals; 2) a developmental neurotoxicity (DNT) study with comparative GS activity measurement in the liver, kidneys, and brain of the pups and mothers; 3) an acute neurotoxicity study in rats with glufosinate ammonium (only) with adequate dosing as per guideline; 4) additional data to confirm that liver and kidney changes observed in the absence of histopathological changes are an adaptive response and not an adverse effect; and 5) a 28-day inhalation toxicity study in rats with glutamine synthetase activity measurements in brain, kidney, liver and lung. The HIARC recommended a 10X Database Uncertainty Factor to account for the lack of these data (TXR No(s): 0050900, 0051833).

In response to HIARC's request, the registrant (Bayer Crop Science) has requested waivers of the oral toxicity studies (1-4) listed above and has submitted data to support the waiver requests (MRID Nos. 46755101; 46755102; 46755103 and 46755104).

The Agency's responses to the waiver requests are provided in this document.

IV. REGISTRANT'S RATIONALE FOR WAIVERS AND AGENCY'S RESPONSE

1. Comparative measurements of glutamine synthetase (GS) activity in the brain, kidney and liver in young and adult animals;

Registrant's Rationale (MRID No. 46755101):

- The Registrant contends that this study should be waived based on the results of a literature study. In this study, similar levels of brain GS inhibition were seen between 10 and 90 day old rats following an intraperitoneal injection of 150 mg/k of MSO. MSO and GA are structurally similar and this supports that a sensitivity difference based on GS

inhibition would not be anticipated with GA.

Agency's Response

- Based on the available toxicological database, EPA agrees with the registrant that the measurement of GS is not a critical endpoint for regulating the chemical. This decision is based on the fact that GS inhibition found at low doses is not associated with any clinical signs of neurotoxicity nor with biologically or toxicologically significant target organ toxicity in the liver, kidney and brain. It takes high doses to induce clinical signs of toxicity following single and repeated dietary exposures. Additionally, the Agency has determined that the brain morphometric changes seen in the offspring at the lowest dose in the DNT would be used for overall risk assessment. Therefore, the Agency is not requiring a comparative assay in young versus adult animals.

2. A developmental neurotoxicity (DNT) study with comparative GS activity measurement in the liver, kidneys, and brain of the pups and mothers;

Registrant's Rationale (MRID No. 46755101):

- The Registrant contends that the Agency's request for inclusion of GS measurement in the DNT was received after the initiation of the study. Additionally, the only treatment-related finding in the DNT is a decrease in the mean length of the ventral limb of the dentate hilus in both sexes at the low dose (200 ppm; 14 mg/kg/day). Except for this one parameter no other treatment-related effects (functional or behavioral) were seen at this dose. It was further postulated that based on the repeated (dietary) exposure studies of various durations an effect on brain GS activity might be anticipated at doses higher than the mid-dose (1000 ppm; 62 mg/kg/day) in the DNT. However, no clinical signs or FOB changes were seen at any dose including the high dose (4500 ppm; 292 mg/kg/day) in the offspring. This is consistent with the results of the other studies in which no clinical signs were seen at levels inducing moderate GS inhibition in the brain. In these studies, a 10%-20% inhibition of GS in the brain was seen at dietary levels of approximately 26 and 64 mg/kg/day and no evidence of cumulative effects were observed. Additionally, no biological consequences of the inhibition were seen in terms of any other measured parameters including histopathological examinations of the perfuse tissues (MRID 40345626; 45179103. 45179101; 40345607).

Agency's Response:

- Based on the available data, the Agency concurs with the Registrant and grants a waiver for a DNT.

3) An acute neurotoxicity study in rats with glufosinate ammonium (only) with adequate dosing as per guideline

Registrant's Rationale (MRID No. 46755102):

- The oral LD50 is 2000 mg/kg in males and 1620 mg/kg in females. The database contains studies that evaluated the acute effects of GA following single oral administration to rats at doses ranging from 10 to 1600 mg/kg. No treatment-related effects were seen at doses up to 100 mg/kg. At 200 mg/kg, piloerection and enhanced activity were seen. GA at doses above 800 mg/kg, caused GS inhibition and clinical signs of CNS intoxication. GS inhibition was completely reversible in the brain and kidneys with clear signs of recovery in the liver. (MRID 40345623; 40345625; 45190703; 45190704; 00142431; 00142432). These studies demonstrated a clear pattern of neurotoxicity and that brain GS inhibition occurs only at high doses (close to the LD50 dose) compared to the current regulatory dose (NOAEL=6.3 mg/kg/day) for acute dietary risk assessment. Therefore, conducting another acute neurotoxicity study would not impact risk assessment and would be contrary to animal welfare standards.

Agency's Response:

- The Agency concurs with the Registrant and grants a waiver for a new acute neurotoxicity study.

4) Additional data to confirm that liver and kidney changes observed in the absence of histopathological changes are an adaptive response and not an adverse effect;

Registrant's Rationale (MRID No. 46755103):

- The toxicity database is extensive and contains a number of dietary studies conducted in mice, rats and dogs ranging from short term (4 weeks), subchronic (13 weeks) and chronic (up to 2 years) exposures. These studies evaluated clinical pathology (hematology, clinical chemistry and urinalyses), organ weights, gross and histopathology to identify potential liver and kidney toxicity. GS activity was altered in the liver and kidney of rats; however, GA did not adversely affect the performance of the whole test organism even after subchronic or chronic exposures in dogs (1-year) and rats (2-years). Treatment-related increases in kidney weights were not accompanied with biologically or toxicologically significant adverse effects. Specific liver and kidney function tested in both rats and dogs showed no adverse effects on the normal physiology of the two target organs. HIARC had concluded that the specific changes in the GS activity in the liver and kidney were adaptive rather than adverse effects. Additionally, GS measurement in rodent kidney has no relevance to humans since the enzyme activity is not expressed in human kidney.

Agency's Response:

- The Agency concurs that no additional data are required to confirm that liver and kidney changes observed in the absence of histopathological changes are an adaptive response and not an adverse effect.

5) A 28-day inhalation toxicity study in rats with glutamine synthetase activity measurements in brain, kidney, liver and lung

Registrant's Rationale (MRID No. 46755104):

- The Registrant contents that the current requirement of a dust/mist respirator mitigates the risk to MOEs of greater than 2500 and all MOEs without a respirator exceeded the level of concern established by HIARC and thus it meets HED SOP 2002.01, Guidance: Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies, 15 August, 2002.

Agency's Response:

The Registrant has submitted a 28-day inhalation study (MRID 47058101) which has been classified as Acceptable/Non-guideline since the study did not meet guideline requirements (only two concentrations were tested as opposed to three) and more importantly, GS activity was not measured in the brain, kidney, liver and lungs (TXR No. 0053314). Additionally, the Agency concurs that the conditions stipulated by the Registrant meet the Waiver Criteria specified in the HED SOP and therefore grants the waiver for this study.

MRID Summary Table

Study Type	MRID	Comments
Waiver for a comparative measurements of GS activity in the brain, kidney, and liver in young and adult animals	46755101	No DER
Waiver for a developmental neurotoxicity (DNT) study with comparative GS activity measurement in the liver, kidneys, and brain of the pups and mothers	46755102	No DER
Waiver for an acute neurotoxicity study in rats with glufosinate ammonium	46755103	No DER
Waiver for a 28-day inhalation toxicity study in rats with glutamine synthetase activity measurements in brain, kidney, liver and lung.	46755104	No DER

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